REVIEW

A Systematic Review of the Impact of Dietary Sodium on Autoimmunity and Inflammation Related to Multiple Sclerosis

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ABSTRACT

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system. Current research into potential causes, risk factors, and treatment is largely based around the immune response involved in the pathophysiology of the disease, including factors that contribute to the augmentation of this immune response. This review aimed to determine the role of sodium as a risk factor for increased autoimmunity and inflammation in relation to MS pathogenesis. This systematic review searched the Scopus, MEDLINE, and PubMed scientific databases for studies related to MS and sodium. Studies were included if they addressed sodium intake and MS but were not limited to a disease type or to a study design. Study quality was assessed through the use of the quality rating checklist of the Academy of Nutrition and Dietetics. A total of 12 studies were included in the review, including human, animal, and cellular studies. The studies related to the proinflammatory effect of sodium, the blood-brain barrier, and an effect on autoimmunity. The data presented throughout this review provide insight into the emerging evidence base for sodium intake as a risk factor for MS disease progression and potentially onset of disease. More studies are needed to determine if the influence of sodium is as a single nutrient or has a combined effect as part of an overall eating pattern. This review was registered at PROSPERO as CRD42016039174. *Adv Nutr* 2019;10:902–910.

Keywords: multiple sclerosis, dietary sodium, inflammation, autoimmunity, experimental animal encephalomylitis

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) and current research into potential causes, risk factors, and treatment is based around the pathophysiology of the disease, including factors that contribute to the augmentation of the immune response (1). Several studies and reviews of the literature have described environmental factors that may contribute to inflammation and autoimmunity in relation to MS, including cigarette smoking, low vitamin D status due to inadequate sunlight exposure (2), and past exposure to the Epstein-Barr virus (3). The majority of the studies that have identified these potential risk factors are epidemiologic in nature. Emerging evidence is now arising in relation to lifestyle-related factors and MS, including intake of various dietary components. In terms of dietary risk factors for MS onset and progression, single nutrients have been identified, including high intakes of saturated fats, and poor intake of ω-3 (n–3) PUFAs, as well as a lack of specific antioxidant components (4, 5).

More recently, high sodium intake has also gained attention as a potential dietary risk factor for the onset and progression of MS (6). Together, these nutrients constitute a Western-style diet—high in saturated fat, added sugars, and sodium, and low in anti-inflammatory PUFAs such as ω-3 (7). Also implicated is a pattern of poor fruit and vegetable intake related to a low intake of a variety of antioxidants (8). Studies suggest Western-style diets may contribute to the development of autoimmunity via low-grade systemic inflammation (9). There have been a number of proposed mechanisms that may explain this increased inflammation. Research suggests the inflammation may be related to obesity that has developed secondary to consuming a Western-style diet long term, where inflammatory mediators are increasingly produced due to overexpression of adipokines from adipose tissue (10).

Mechanisms of increased inflammation may also relate to the over- or underconsumption of specific nutrients rather than the dietary pattern as a whole. These mechanisms

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Abbreviations used: CNS, central nervous system; EAE, encephalomyelitis; MS, multiple sclerosis; NHMRC, National Health and Medical Research Council; ROS, reactive oxygen species; Tregs, T-regulatory cells.

suggest that increased reactive oxygen species (ROS) in the body cause oxidative stress leading to tissue damage, including increased release of proinflammatory cytokines and increased inflammation (11). Antioxidant compounds found in a variety of foods, including fruits and vegetables, act within the body to reduce this oxidative stress, implying poor dietary variety or a lack of fruit and vegetables in the diet may lead to increased inflammation via ROS (12).

Similar to the effects of poor dietary variety leading to inflammation via oxidative stress, recent studies have also suggested high dietary sodium may lead to an increased inflammatory response. Despite a range of evidence to suggest that sodium has an influence on immune cell activity (13, 14), it is questioned if this is due to excess sodium excretion and homeostatic control by the kidneys. In response to this, studies have indicated that sodium build-up can occur interstitially in areas such as the skin and lymphoid tissue (15, 16). This suggests that despite tight regulation of extracellular sodium concentration via the kidneys, sodium accumulation can still occur in the human body when exposed to a high-salt diet and consequently affect immune cell function (17).

Various cytokines and their release by activated T cells have been observed in MS and its associated inflammation (18); of particular interest are the proinflammatory Th17 cells that produce IL-17, which is highly upregulated in chronic CNS lesions in individuals with MS (19). Lesions are sites of demyelination and indicative of MS. Increased infiltration of macrophages and T cells into the CNS of MS patients, particularly around areas of multifocal demyelination, are a substantial indicator of disease severity observed both in human MS presentation as well as in animal models of the disease (20). Similarly, monocyte numbers in the blood of persons with MS, particularly during disease exacerbations, have been shown to be significantly higher than in the general population (21).

Experimental autoimmune encephalomyelitis (EAE) is considered as an appropriate animal model for human MS. EAE is mediated by $CD4^+$ T cells and results in mononuclear cell inflammation, ultimately leading to demyelination of the CNS. EAE can represent either a relapsing-remitting or a chronic-progressive disease course and is therefore commonly used in mechanistic research related to MS (22, 23).

Although mechanistic research has been undertaken for MS, more recent studies have included human intervention and observational studies. The influence of dietary sodium on MS risk and progression has not been extensively studied in humans, but it is nevertheless of interest to determine whether excess intakes of single nutrients, in this case sodium, can augment the autoimmune response and, therefore, increase inflammation in spite of the effects of inflammation related to obesity.

This review aimed to determine the role sodium plays in increased autoimmunity and inflammation in relation to MS pathogenesis across cellular, animal, and human study designs to demonstrate progression of the research.

Methods

This systematic literature review was registered with PROSPERO as CRD42016039174, and was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (24), and guided by the National Health and Medical Research Council (NHMRC) (25) process for systematic literature review. The primary outcome of the review was to determine the impact of sodium on inflammation and the autoimmune response related to MS pathogenesis. Literature searches were undertaken in July 2018 to update a review undertaken 2 y previously that was based on the use of the Scopus, MEDLINE, and PubMed databases. The search strategy used a combination of the following keywords with Boolean operators as appropriate: sodium, salt, inflammat∗, autoimmun∗, autoimmun∗, multiple sclerosis. Inclusion criteria for identified articles included studies published in the English language and those in a peer-reviewed journal. No limits were applied to the study designs or study populations in order to describe the progression of MS research related to sodium. These inclusion criteria were not overly restrictive as informed by a prior pilot search. Articles were excluded if they did not meet the inclusion criteria and were not deemed relevant to the research aims. A manual search of included articles was undertaken as a final step to ensure inclusion of all relevant research.

Articles were initially screened by title and abstract followed by a full-text review. The screening was undertaken by one researcher (EM) and repeated by two separate independent researchers (KT, ES). The studies were compiled in a summary table according to developed themes categorized by study population (**Tables 1**–**3**). Data was extracted by one researcher (EM or KT) and checked by two researchers (ES, YP). Some of the studies addressed multiple themes and were therefore repeated in the tables with the relevant data extracted to each theme. The NHMRC levels of evidence (25) were considered for all included human studies and studies were assessed for quality and bias with the use of the Academy of Nutrition and Dietetics Quality Assessment Checklist (26).

Results

A total of 367 articles were screened for inclusion. Three additional articles were located via the manual search (27–29). **Figure 1** shows the flow of study selection in terms of inclusion and exclusion criteria. A total of 12 articles were deemed eligible to be included in the qualitative synthesis. The study population of extracted articles included humans ($n = 6$) (27–32), animal ($n = 6$) (17, 33–37), and experimental studies conducted at the cellular level ($n = 6$), with some overlap between articles (17, 32–36). Ten studies (17, 28–30, 32–37) were quality rated as positive and two studies rated as neutral (27, 31). Six studies (27–32) were categorized as level III-2 (cohort studies) according to the NHMRC hierarchy of evidence (25), whereas the level of

TABLE 1 Characteristics of studies included: experimental cellular studies[1]

Reference	Population	Comparator	Outcome	Results	Quality[2]
Augmentation of the inflammatory T cell response and cytokine production					
Hammer et al. 2017 (33)	Naïve $CD4^+$ T cells	T cells treated with 40 nM sodium and/or 250 μM LA	Differentiation of T cells and production of cytokines	Both sodium + LA enhanced differentiation of Th17 cells and increased proinflammatory cytokines and genes	P
Hernandez et al. 2015 (34)	Treg $CD4^+$ cells	High-sodium media/normal media on Treg cell function	Suppressive function of Treg cells.	Treg suppressor decreased in high-salt media**	P
Kleinewietfeld et al. 2013 (17)	Naïve $CD4^+$ T cells	Th17-inducing cytokines in high sodium media (40 mM)	Induction of proinflammatory cytokines IL-17F, IL-2, TNFα, IL-9	High sodium induced more pathogenic Th17 cell and proinflammatory cytokines	P
Wu et al. 2013 (36)	Naïve T cells	T cells activated in additional 40 mM sodium	Upregulation of Th17-specific genes	Th17-specific genes upregulated in presence of sodium	P
Effect of sodium on monocyte numbers and proinflammatory phenotype production					
Hucke et al. 2016 (35)	Bone marrow–derived macrophages	High-sodium media	Shift towards proinflammatory phenotype in human monocytes	Macrophages shift toward proinflammatory M1 phenotype in high-sodium media*	P
Zhou et al. 2013 (32)	Human circulating monocytes	Monocytes incubated with/without additional (25 mM) sodium	Expansion of $CD14^{++}CD16^+$ monocytes	Number and percentage of monocytes increased with high sodium	P
The effect of sodium on EAE and BBB breakdown					
No cellular studies					
Effect of sodium on autoimmunity and MS onset and progression					
No cellular studies					

[1]Values are significant at: *$P < 0.05$, **$P < 0.01$. BBB, blood-brain barrier; EAE, experimental autoimmune encephalomyelitis; LA, lauric acid; MS, multiple sclerosis; Treg, T regulatory cell.
[2]Quality rating: P, positive; 0, neutral; N, negative.

evidence was not applicable to the remaining 6 studies (17, 33–37) due to the nature of their experimental study design.

Augmentation of the inflammatory T cell response and cytokine production

Five included studies addressed the influence of a high-sodium diet compared with a standard sodium diet on the activity of inflammatory T cells and cytokine production in vitro and in vivo. The studies all found an association between a high-salt diet or high-salt environment in experimental media and an augmentation of the T cell response (17, 27, 34, 36, 37). One study focused on the factor partially responsible for the defective self-tolerance commonly observed in MS, namely IFNγ-secreting forkhead box transcription factor ($Foxp3^+$) T regulatory cells (Tregs) (34). IFNγ is a cytokine involved in innate and adaptive immunity and has been implicated in neuroinflammation related to MS (38). In vitro, the immunosuppressive function of human Tregs was inhibited when exposed to high-salt media (40 mM sodium chloride, herein referred to as sodium) compared with regular media ($P = 0.0012$). In vivo, the researchers examined Treg function by exposing mice to either a normal (0.4% of sodium) or a high-sodium diet of 8% sodium in chow and 1% sodium in drinking water to examine the effect on the autoimmune process. Mice exposed to a high-sodium diet developed a more severe disease with faster onset, and also had an increased percentage of IFNγ-secreting Tregs than those on the normal diet ($P = 0.0092$) (34). Another study (37) also exposed mice to a high-sodium diet and found no significant effect on numbers of $Foxp3^+$ Tregs (37).

Increased numbers of proinflammatory cytokines, such as TNFα, IL-12, IL-6, and IL-23, were found in 4 included studies that investigated high-sodium conditions (35). The animal study found larger numbers of proinflammatory mediators in the CNS of the high-sodium diet group (35), whereas 2 cellular studies (17, 36) observed altered T cell response. These results were replicated in a human population where 6 healthy male adults had their dietary sodium intakes manipulated for 205 d (27). The results showed that a decrease in sodium intake was associated with a decrease in proinflammatory cytokines (IL-6 and IL-23) and an increase in the anti-inflammatory cytokine IL-10 (27).

Effect of sodium on monocyte numbers and proinflammatory phenotype production

Two included studies used experimental methods to determine whether sodium contributes to increased macrophage infiltration into the CNS, increased numbers of monocytes, and, therefore, increased proinflammatory mediator production and expression. A cellular study of murine and human cells under high-sodium conditions (35) found that after the mice were exposed to a high-sodium diet, they showed increased macrophage infiltration into the CNS as well as increased expression of markers of the inflammatory

TABLE 2 Characteristics of included animal studies[1]

Reference	Population	Comparator	Outcome	Results	Quality rating[2]
Augmentation of the inflammatory T cell response and cytokine production					
Hammer et al. 2017 (33)	C57BL/6 J mice	Normal chow (0.4% sodium, 4.2% fat) or high sodium (4%) or high fat (30.9% fat) or high sodium and fat (4% and 30%)	Upregulation of Th1 and Th17 genes, EAE aggravation, production of proinflammatory cytokines	High sodium and sodium + LA diet aggravated EAE course, increased T cell infiltration, decreased Treg cells, increased Th1 and Th17 genes	P
Hernandez et al. 2015 (34)	Immune-deficient NSG mice	0.4% sodium or 8% sodium and water (1% sodium)	Development of xGv-HD after 40 d of prescribed diet and percentage of IFNγ + producing Tregs	High salt increases percentage of IFNγ + Tregs,** more severe disease and faster onset	P
Kremenstov et al. 2015 (37)	SJL/JCrHsd mice ($n = 16$) and C57BL/6 mice ($n = 16$)	High sodium (4%) and tap water (1% sodium)	Augmentation of T cell response	No augmentation of T cells observed	P
Hucke et al. 2016 (35)	C57BL/6 mice	Standard chow and tap water or high-sodium chow (4%) and water (1% sodium).	Production of proinflammatory myeloid cells, increased cytokine production, EAE aggravation	Aggravated EAE course, *** increased macrophage infiltration, and myeloid proinflammatory mediators	P
Effect of sodium on monocyte numbers and proinflammatory phenotype production					
No animal studies					
The effect of sodium on EAE and BBB breakdown					
Kleinewietfeld et al. 2013 (17)	C57BL/6 mice ($n = 12$)	High-sodium diet (4%) and water (1% sodium)	EAE onset and disease severity	High-salt diet accelerated EAE onset, increased severity	P
Wu et al. 2013 (36)	C57BL/6 mice—wild type or SGK1 deficient	Mice fed normal or high sodium diet	Development of proinflammatory Th17 cells, EAE onset and severity	Increased EAE severity (mean clinical score) and higher Th17 cells*	P
Kremenstov et al. 2015 (37)	SJL/JCrHsd mice ($n = 16$) and C57BL/6 mice ($n = 16$)	High-sodium (4%) diet and low-salt tap water (1% sodium)	Severity of course of EAE determined by physical disability and CNS lesions	High-sodium diet exacerbated EAE in the C57BL/6 mice. Only females affected in SJL/JCrHsd mice. No increased BBB breakdown	P
Hucke et al. 2016 (35)	C57BL/6 mice.	Standard chow and tap water or high-sodium chow (4%) and water (1% sodium)	EAE aggravation	Aggravated EAE course***	P
Effect of sodium on autoimmunity and MS onset and progression					
No animal studies					

[1]Values are significant at: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. BBB, blood-brain barrier; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; LA, lauric acid; MS, multiple sclerosis; Treg, T regulatory cell; xGv-HD; xenogenic graft-versus host disease.
[2]Quality rating: P, positive; 0, neutral; N, negative.

M1 macrophage phenotype. Similarly, human monocytes responded to high-sodium media by also shifting toward this proinflammatory M1 macrophage phenotype and away from an anti-inflammatory M2 phenotype (35). Likewise, the previously mentioned sodium manipulation study (27) observed monocyte numbers positively associated with sodium intake (27), suggesting a relation between sodium intake and an increase in the immune response. A second cellular study replicated this effect but also observed increases in nonclassical and intermediate monocyte subsets implicated in autoimmune disease, including MS (32, 39, 40).

Building on this, a 3-phase dietary intervention was undertaken where a usual diet was followed by a high-sodium diet (15 g/d for 7 d) and then a low-sodium diet (5 g/d for 7 d) (32). Human monocytes were also incubated in normal- or high-sodium media. In both experiments, exposure to high sodium increased numbers of the intermediate monocyte subset $CD14^{++}CD16^{+}$. In the dietary manipulation phase, the numbers of these subsets increased progressively during the high-sodium stage ($P < 0.001$) (32). Together, these studies display notable implications when assessing the effect of sodium on the autoimmune processes underpinning MS.

The effect of sodium on experimental autoimmune encephalomyelitis and blood-brain barrier breakdown

Four studies (17, 35–37) used in vivo methods to determine the effect of a high-sodium diet on the course of EAE in mice. These studies fed a high-sodium or a normal control diet

TABLE 3 Characteristics of included human population studies[1]

Reference	Study design (LoE)	Population	Intervention	Outcome	Results	Quality rating[2]
Augmentation of the inflammatory T cell response and cytokine production						
Yi et al. 2015 (27)	Longitudinal cohort (III-2)	Male adults ($n = 6$), mean 33 y	Changing dietary sodium; 12 g/d, 9 g/d, 6 g/d for 50 ± 10 d each, then 12 g/d for 30 d	Cytokine numbers and types	Low salt intake; decrease in proinflammatory cytokines. Anti-inflammatory cytokine increased in low-salt stage***	0
Effect of sodium on monocyte numbers and proinflammatory phenotype production						
Yi et al. 2015 (27)	Longitudinal cohort (III-2)	Male adults ($n = 6$), mean 33 y	Changing dietary sodium; 12 g/d, 9 g/d, 6 g/d for 50 ± 10 d each, then 12 g/d for 30 d	Percentage monocytes in blood in response to change in sodium	Monocyte numbers higher in high salt stage.*** Monocyte numbers positively associated with salt intake***	0
Zhou et al. 2013 (32)	Cohort study (III-2)	Healthy adults ($n = 20$), mean 29.75 y, BMI 21.92 kg/m^2	Usual sodium, high sodium (15 g/d), low sodium (5 g/d)	Increase in $CD14^{++}CD16^{+}$ monocyte subset numbers	$CD14^{++}CD16^{+}$ monocyte subset increased progressively during high-salt intake phase until numbers plateaued***	P
The effect of sodium on EAE and BBB breakdown						
No human studies						
Effect of sodium on autoimmunity and MS onset and progression in human subjects						
Farez et al. 2015 (30)	Longitudinal cohort (III-2)	Group 1–($n = 70$), 2–cross-sectional sample ($n = 52$) with RRMS	Sodium (<2 g/d, 2–4.8 g/d, >4.8 g/day) and clinical and radiologic MS disease activity	Relapses from recruitment to last follow-up, CUA and T2 lesion load on MRI	IRR for <2 g/d = 1 (P = NA), 2–4.8 g/y = 2.75,** >4.8 g = 3.95.** High-sodium 3.4-fold likelihood for new lesion, average 8 more T2 lesions compared with lower sodium	P
Fitzgerald et al. 2017 (28)	Longitudinal cohort (III-2)	CIS patients ($n = 468$)	Estimated 24-h urinary sodium excretion	Conversion to MS, EDSS, and MRI outcomes	Mean 24-h sodium not associated with conversion to MS, EDSS, or MRI (new lesion, changed T2 volume)	P
McDonald et al. 2016 (31)	Case control (III-2)	Cases ($n = 170$); CIS or RRMS onset <18 y. Controls ($n = 331$) no autoimmune disease	Dietary sodium consumption (mg/d) between cases and controls	Dietary salt intake and pediatric-onset MS risk	Risk of MS not increased with increased or excess sodium intake above AI	0
Nourbakhsh et al. 2016 (29)	Case control (III-2)	RRMS/CIS ($n = 174$) onset <18 y and disease duration <4 y	Dietary sodium density (sodium: energy)	Time to relapse as new or recurrent neurologic symptoms	Sodium not associated with time to relapse (HR per 1 mg/10 kcal: 0.98; 95% CI: 0.91, 1.06). Excess sodium had no decrease in time to relapse (HR: 0.85; 95% CI: 0.54, 1.35).	P

[1]Values are significant at: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. AI, adequate intake; BBB, blood-brain barrier; CIS, clinically isolated syndrome; CUA, combined unique activity; EAE, experimental autoimmune encephalomyelitis; EDSS, Expanded Disability Status Scale; LA, lauric acid, LoE, level of evidence; MS, multiple sclerosis; NA, not available; RRMS, relapsing-remitting multiple sclerosis; Treg, T regulatory cell.
[2]Quality rating: P, positive; 0, neutral; N, negative.

to randomly selected mice. In all studies, mice on the high-sodium diet showed increased EAE disease exacerbation with higher mean clinical scores than the control mice. These results were not without further pathophysiologic observations; 1 study found a significant increase in IL-17A-expressing $CD4^{+}$ cell infiltration into the CNS (17); the second study (36) found a higher number of Th17 cells in the mesenteric lymph nodes and CNS, and a larger percentage of IFNγ-producing T cells in the CNS; and the third study (37) noted that exacerbated disease course was correlated with an enhanced blood-brain barrier breakdown, an occurrence associated with more vigorous MS disease progression (41).

Effect of sodium on autoimmunity and MS onset and progression in human participants

Three human studies related to MS onset and progression in relation to sodium intakes. Two used relapsing-remitting MS (30) whereas the third was applied to pediatric-onset MS. A low intake of sodium was quantified according to the WHO recommendation of <2 g sodium/d (42). Intake was assessed via 24-h urinary sodium excretion methods, the gold standard for assessing intake concentrations (43). The results showed that individuals consuming high-sodium intakes had an incidence rate ratio (IRR) of 3.95 compared with the low-sodium intake group for relapse rate. The average T2 lesion counts were 14.13 in the high-sodium group compared with 6.45 in the low-sodium group. The second study replicated the first in a cross-sectional analysis and obtained similar results (30). Although these two studies looked at MS progression, the effects of sodium intake on onset of the disease with a pediatric case-control study was also addressed (31). Sodium intake was assessed via the Block Kids Food Screener tool for assessing dietary intake in children aged 2–17 y (44). The results indicated no higher

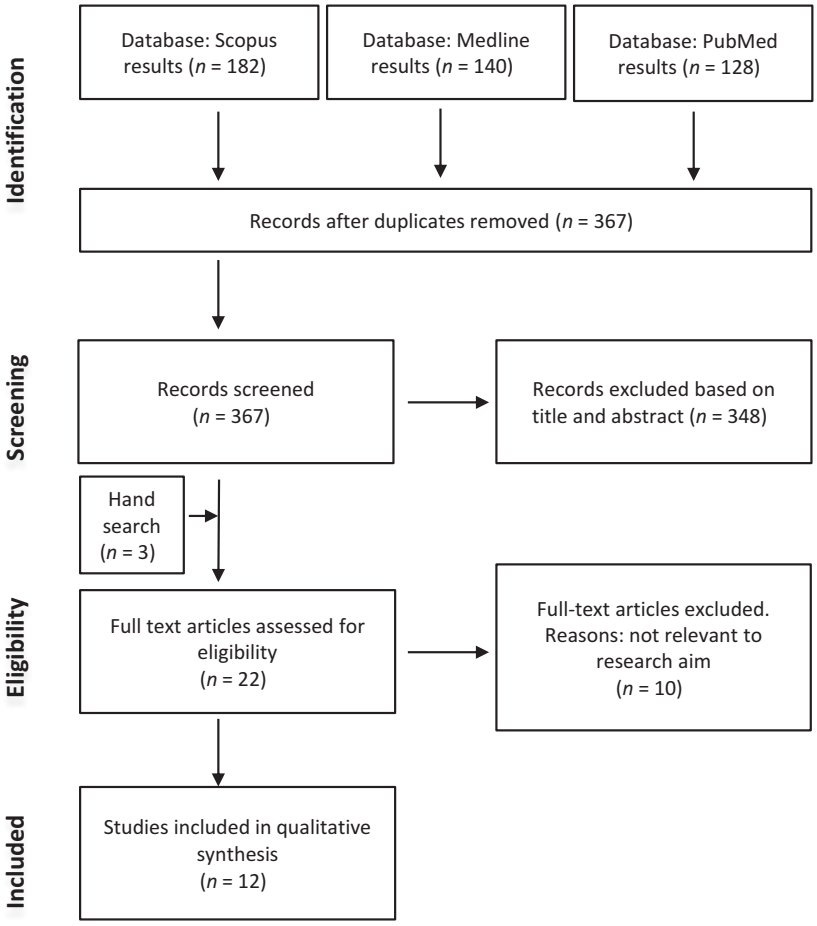

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of included studies.

risk of MS development for increased sodium intakes, and excess sodium intake above the Adequate Intake (US) level for age and gender was not associated with an increased risk of MS development (31).

Discussion

The studies included in this review exhibit varying levels of evidence towards sodium as a factor for increased inflammation and autoimmunity related to MS (**Figure 2**). This research reveals promising data about how sodium may influence MS pathogenesis through exacerbation of the immune response and therefore inflammation involved in the disease course. Although other reviews have been published in relation to sodium and MS, these reviews have mainly focused on the related mechanisms. This review has aimed to synthesize the evidence ranging from cellular through to human clinical studies to provide insight into this growing area of research.

As evidenced by this review, the pathophysiology behind MS is complex. It is well established that a variety of immunomodulatory molecules contribute to the onset and

	T-cell response	Cytokine production	Monocyte numbers	Pro-inflammatory phenotype	EAE course	Disease onset	Disease progression
Cellular	++++	++	+	+			
Animal	++++	+			+++++		
Human		+	++			+	+++

FIGURE 2 Summary of outcomes related to study population. + represents study outcome. EAE, experimental autoimmune encephalomyelitis.

progression of the disease (38). Many of the in vitro experimental studies surrounding these immunologic factors provide a suitable lead for further research. Although conversion of sodium concentration in experimental media is difficult to translate to human consumption, the results provide an indication that increases in sodium may have an effect on immunomodulatory cell numbers and activation, particularly those linked to autoimmune activity. Of particular interest are the findings by Kleinewietfeld et al. (17), who noted that the induction of IL-17A from naïve $CD4^+$ cells occurred in a dose-dependent manner. The range found to be effective in amplifying the inflammatory response (17) aligns with the mechanistic understanding for sodium.

The results exhibited in the included in vitro studies provide evidence that sodium is likely to affect the immune response, as a variety of immunomodulatory cells were examined and all showed alteration with increased sodium concentration. T helper cells, Tregs (suppressor cells), cytokines, and myeloid cells are all included in the complex autoimmunity behind MS pathogenesis (45) and were all affected by increases in sodium. The included in vivo studies demonstrate that the complex activity of T cells and the upregulation of their specific genes are integral to increased autoimmunity. The results exhibit an inextricable link between high sodium conditions and augmentation of the T cell response in the CNS (46). The included studies were able to show increased macrophage infiltration into the CNS, as well as increased monocyte numbers in the blood of healthy individuals when exposed to a high-sodium diet. Importantly, the increased monocytes observed in these studies were often shifting towards a proinflammatory phenotype, which has been associated with autoimmune disease, including MS (21).

Induction of EAE was seen in five of the included animal studies (17, 33, 35–37) as an appropriate method of replication of results. This method allowed researchers to translate the effects of high sodium on immune cell function to a physical representation of these effects. EAE was exacerbated upon intervention with a high-sodium diet in all studies. These amounts would correlate to exceptionally high sodium intakes in a human population, to a point of physiologic implausibility. To support the use of high amounts of sodium, the researchers were mimicking a long period of excessive sodium consumption. The relation between the lifespan of humans and mice has indicated that 3–4 wk in the experimental mice represents long-term intake in a human. These studies exhibited the effect of high sodium on the immune response relating to MS that had previously been observed in cellular studies; however, here it was more evident that exposure to a high-sodium diet affects disease outcomes in a mouse model of MS as well as affecting the cellular response.

The 6 human studies that were included in this review provide insight into the role of dietary sodium in MS and are useful in examining the results obtained experimentally. Farez et al. (30) found the mean estimated daily sodium intake of their population ($n = 70$) was 4.12 g of salt, or ~1650 mg of sodium. In Australia, the population average daily salt intake is 5.5 g (2150 mg sodium) (47). Male participants had significantly higher intakes of salt than female (30) (5.3 g compared with 3.78 g, respectively), a noteworthy observation considering the accelerated MS disease progression in men. However, the study did not adjust for total energy intake and it is unknown if salt intakes were proportionate to total dietary intake.

Studies included in the review found an association between high sodium intake and either worsened MS disease activity or increased autoimmune responses. Farez et al. (30) found a positive correlation between salt intake and relapse rate ($n = 70$) (30). Despite the relatively small sample size, these results exhibit an interesting link between high sodium intakes and MS disease activity. Healthy adults were also used rather than those with already existing MS (27). The advantage of this resided in the environmentally controlled conditions of the study. The results showed a positive association between monocyte numbers and sodium intake, and that anti-inflammatory cytokines were more prevalent in the low-sodium diet stage (27). Although the study cannot exhibit specific relations between sodium intake and MS, it effectively represents in vitro experimental study results in humans.

Lastly, the pediatric study presented contradictory results. The study observed intake and found no significant differences between cases and controls for higher sodium intakes, or for sodium intakes above nutrient reference values (31). This is the only study included that observed solely MS onset rather than disease exacerbation or progression, and this may be a contributing factor as to why sodium intake was not associated with MS. Another consideration was the age of participants; with a mean age of 15.2 y it is important to consider a possible difference in the pathophysiology of MS in younger individuals. There are similarities between the presentation and pathophysiology of adult and pediatric MS, however, and it has also been recognized that there are distinguishing features of pediatric MS in terms of clinical presentation and disease course. It is also recognized that there is reduced time for environmental exposure, providing further evidence that environmental exposures may play a different role in the onset of pediatric MS compared with in the adult population (48).

Although independent researchers assessed the included eligible articles, having 2 reviewers screening the studies in parallel and reaching consensus may have further strengthened the study. Furthermore, it was not possible to define the type of MS for this review due to the limited evidence but it is expected that there may be differences in the effects on inflammation seen between the different types of the disease due to the differing progression that occurs.

In conclusion, the data presented throughout this review provide awareness of the possibility of dietary sodium intake as a risk factor for MS disease progression and potentially the onset of disease. Although it is of interest to address this through increased human studies, concerns arise in relation

to reverse causality concerning the onset and progression of MS. Studies that explore the relation of a dietary pattern that is also high in dietary sodium could also result in exacerbations of MS symptoms. The included studies exhibit the impact of sodium at a cellular level, providing insight into potential mechanisms behind the disease. The results also show the physical effects of increased sodium on MS exacerbation and autoimmune cellular proliferation in animals and humans. Although causality cannot be assumed from the data available, current research in the area provides evidence to warrant further research into the area to better understand the role of sodium intake in autoimmunity and inflammation related to MS pathogenesis.

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